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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/569,812	02/10/2006	Ian Holmes	PB60441	6556

20462 7590 01/03/2008

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EXAMINER	
LAO, MARIALOUISA	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
01/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/569,812	HOLMES ET AL.	
	Examiner	Art Unit	
	M. Louisa Lao	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,7,9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 7* is/are rejected.

7)☒ Claim(s) *4,5 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: a)Notice to Comply;b)Applicant 10/16/07 3page submission.

DETAILED ACTION

1. Please find below and/or attached an Office communication concerning this application or proceeding.

Response to Arguments

2. Applicants' submission of the CRF on 10/16/07 in order to comply with the requirements of 37 C.F.R. 1.821-1.825 is acknowledged. However, the CRF is flawed technically and not entered for the reason(s) set forth on the attached Notice to Comply With the Sequence Rules or CRF Diskette Problem Report. Furthermore, applicant has not provided a separate paper copy of the Sequence Listing.

The addresses below are effective 5 June 2004. Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (<http://www.uspto.gov/ebc/efs/downloads/documents.htm>, EFS Submission User Manual - ePAVE)

2. Mailed to:

Mail Stop Sequence
Commissioner for Patents
P.O. Box 22313-1450
Alexandria, VA 22313-1450

3. Hand Carry, Federal Express, United Parcel Service or other delivery service to:

U.S. Patent and Trademark Office
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Customer Window
Randolph Building

3. Applicant's arguments, see REMARKS, filed 8/2/07, with respect to claims 1, 4, 5, 7 and 9 have been fully considered and are persuasive. The rejection of 1, 4, 5, 7 and 9 under 35 U.S.C. 102(b) has been withdrawn.

4. Applicants' arguments via amendment, see REMARKS, filed 8/2/07, with respect to claim 7, have been fully considered; but are not persuasive. The rejection of claim 7 under 35

U.S.C. 112, first paragraph, in the Office Action mailed 4/5/07, is reinstated, for reasons discussed below.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **Claim 7 is rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of inhibiting MMP-12, does not reasonably provide enablement for treating any inflammatory disease or autoimmune disorder. The specification does not enable the person skilled in the art of clinical pharmacy, to make the invention commensurate in scope with these claims. The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in the art, g) the predictability or unpredictability of the art, and, h) the breadth of the claims.

7. In the present case, the important factors leading to a conclusion of undue experimentation are the absence of any working example of a method for the treatment of a human or animal suffering from an inflammatory disease or an autoimmune disorder, the lack of predictability in the art, the amount of direction and guidance provided and the broad scope of the claim.

8. ***a) the nature of the invention*:** Claim 7 is recites method for the treatment of a human or animal suffering from *an inflammatory disease or an autoimmune disorder* comprising administering to said subject an effective amount of a compound of claim I.

b) ***the breadth of the claims:*** Claim 7 is recites method for the treatment of a human or animal suffering from *an inflammatory disease or an autoimmune disorder* comprising administering to said subject an effective amount of a compound of claim I. This is broad. The claim, as written encompasses any and all inflammatory diseases and any and all autoimmune disorders. Further, on page 14, the specification exemplifies, without limit, a large, varied and unrelated number of diseases that are encompassed by these terms.

c&e) state and predictability of the art. Compounds of the structure as recited in Formula (I) are known, see Muller et al. (US6380239, US`239). Prior art made of record further show that MMP-12 belongs to a family of compounds which play diverse roles physiologically. Illustratively, Reiter (US6087392, US`392) teaches that MMP subfamily of enzymes currently contains seventeen members (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20). Reiter teaches that the MMP's are most well known for their role in regulating the turn-over of extracellular matrix proteins and as such play important roles in normal physiological processes such as reproduction, development and differentiation. In addition, Reiter teaches that the MMP's are expressed in many pathological situations in which abnormal connective tissue turnover is occurring. For example, MMP-13 an enzyme with potent activity at degrading type II collagen (the principal collagen in cartilage), has been demonstrated to be over-expressed in osteoarthritic cartilage (Mitchell, et al., J. Clin. Invest., 97, 761 (1996)). Other

MMPs (MMP-2, MMP-3, MMP-8, MMP-9, MMP-12) are also over-expressed in osteoarthritic cartilage and inhibition of some or all of these MMP's is expected to slow or block the accelerated loss of cartilage typical of joint diseases such as osteoarthritis or rheumatoid arthritis (column 2 lines 23- 42). However, the precise role that any particular MMP plays in a given disease is complex and not well-known or accepted in the art. Shapiro (Thrombosis and Homeostasis, 82: 846-849, 1991) for example discusses the role that MMP-12 may play in tissue destruction and specifically state that findings in animal models may not be predictive of any given human state. Furthermore, Newby (Current Opinion in Lipidology, 17:556-61, 2006) provide evidence that MMP-12 can have opposite effects within the same system. Therefore, while metalloproteinases in general are known to play some role in the inflammatory process, the state of the art does not support the conclusion that inhibition of any particular MMP, specifically MMP-12, would be reasonably expected to predictably have a therapeutic effect on all inflammatory diseases or diseases with an inflammatory aspect or on any autoimmune disorders.

d)the relative skill of those in the art: the skill is high.

e&f)amount of guidance present and working examples. Since the compounds of Formula I and Ia are replete with substituents effectuating to different structures with invariable distinct characteristics, the quantity of experiments corresponding thereto, would likewise be numerous.

g) quantity of experimentation needed. There are no working examples of method for the treatment of a human or animal suffering from an inflammatory disease or an autoimmune disorder. Claim 7 is drawn to "method for the treatment of a human or animal suffering from an inflammatory disease or an autoimmune disorder", yet the various examples presented are found

deficient to encompass inflammatory or autoimmune disorders, other than data on page 18 showing that the tested compounds inhibit MMP-12. This data is, however, *in vitro* data of inhibition of enzymatic activity and cannot, absent further guidance, be predictably extrapolated to the treatment of any inflammatory disease or autoimmune disorder. Faced with the numerity of potential inflammatory diseases or autoimmune disorders, one of ordinary skill in the art at time of Applicants' invention would have to do numerous experiments to address a myriad of said disorders, and to test the functionality of the compounds recited therein relative to their efficacy in addressing any or all inflammatory diseases or autoimmune disorders. This amount of experimentation, where the outcome of finding any compound that provides therapeutic benefit is unpredictable and amounts to undue experimentation.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.Cir.1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 3, after the structure of formula (I), claim 1 recites, "provided that R^2 is not" and "except". In line 11, claim 9 recites, "R^3 is OR^6 or NR^8R^9". In line 13, claim 1 recites, "R^6 is H or C_{1-6} alkyl". In line 15, claim 9 recites "R^8 and R^9 each independently is H or C_{1-6} alkyl; or R^8 and R^9 together with the nitrogen atom to which they are attached form a 5- or 6-membered

ring which may optionally includes 1 or more further heteroatoms selected from O, S and N; or physiologically functional derivatives thereof", where Applicants may have intended to amend these limitations, which are no longer part of the structure.

Allowable Subject Matter

11. Claims 4, 5, 9 and 10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MLouisa Lao whose telephone number is 571-272-9930. The examiner can normally be reached on Mondays to Thursdays from 8:00am to 8:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

`mll11152007
MLouisa Lao
Examiner
Art Unit 1621

YVONNE EYLER
SUPERVISORY PATENT EXAMINER
TC1600 GAU 1621

Notice to Comply	Application No. 10/569812	Applicant(s) HOLMES ET AL.	
	Examiner M Louisa Lao	Art Unit 1621	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☒ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-0731 or (571) 272-0951
For CRF Submission Help, call (571) 272-2510
PatentIn Software Program Support
Technical Assistance.1-866-217-9197 or 703-305-3028 or 571-272-6845
PatentIn Software is Available At www.USPTO.gov

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

10/16/07 3 pages
Fwd fr Applicant
Due 11/25/07

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Sequence Listing could not be accepted.

If you need help call the Patent Electronic Business Center at (866) 217-9197 (toll free).

Reviewer: Anne Corrigan

Timestamp: Tue Oct 16 09:38:10 EDT 2007

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****

Reviewer Comments:

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<211> 9

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The above <213> response is invalid: just indicate "Artificial Sequence."

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<223> Fluorescent peptide substrate

Please try to give more information regarding the above <223> response (e.g., source of the genetic material).

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Validated By CRFValidator v 1.0.3

Application No: 10569812 Version No: 1.0

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Output Set:

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Finished: 2007-09-28 12:11:33.125
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Actual SeqID Count: 1

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SEQUENCE LISTING

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WATSON, Stephen Paul

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